



## Dietary Supplements and Herbal Medicines Initiative

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Medicinal herbs are among our oldest medicines and their increasing use is evidence of public interest in alternatives to conventional medicine. Herbal medicines are a multi-billion dollar industry in the United States with more than 1500 botanicals sold as dietary supplements or ethnic traditional medicines. Herbal dietary supplements are not subject to Food and Drug Administration (FDA) pre-market approval to assure their safety or efficacy.

The National Toxicology Program (NTP), held a workshop on herbal medicines in 1998 in response to public concerns regarding the use and efficacy of medicinal herbs and to recent nominations of these products for study. Recommendations from the workshop included a call for (1) more research on herbals, (2) the identification and standardization of product ingredients by industry, and (3) increased consumer education through package inserts.

Staffs at both the NIEHS and NCTR are actively working with the National Institutes of Health (NIH) Office of Dietary Supplements, the Center for Food Safety and Nutrition of the FDA, the academic community, and others to conduct research that will address deficiencies in our knowledge about dietary supplements and herbal medicines and their potential toxicities.

Dietary supplements, containing biologically active constituents found in some herbs and herbal extracts, continue to be nominated and selected for study by the NTP, including some of the most common dietary supplements used by consumers in the United States.

Studies have been designed for many dietary supplements and herbal products that focus on the characterization of potential adverse health effects, including general toxicity associated with short-term high-dose exposure and/or long-term exposure to lower doses, as well as system specific toxicities including reproductive toxicity, neurotoxicity, cardiovascular toxicity and immunotoxicity.

NTP evaluations of these dietary supplements include extensive physico-chemical characterizations of the materials and their constituents, *in vivo* Good Laboratory Practices toxicological studies, mechanism-based investigative studies, evaluation of pharmacokinetics, and use of *in vitro* models for evaluation of biological interactions and mechanisms of action.



## Dietary supplements and herbal medicines under evaluation by NTP include:

Aloe vera gel	Widely used herb for centuries as a treatment for minor burns and is increasingly being used in products for internal consumption.
Bitter Orange ( <i>Citrus aurantium</i> )	Bitter orange peel and its constituent synephrine have adrenergic activity and may result in cardiovascular or other adverse effects similar to those induced by ephedra alkaloids.
Black cohosh	Used to treat symptoms of pre-menstrual syndrome, dysmenorrhea and menopause.
Dong quai ( <i>Angelica sinensis</i> root) and extract	Use as an antispasmodic or blood purifier and for reduction of pain, dilation of blood vessels, and stimulation, as well as relaxation of uterine muscles.
<i>Garcinia cambogia</i>	<i>Garcinia cambogia</i> is marketed as an ephedra-free diet aid and there is consumer exposure through increasing dietary supplement use.
<i>Ginkgo biloba</i> extract	<i>Ginkgo</i> fruit and seeds have been used medicinally for thousands of years to promote improved blood flow, and short-term memory and to treat headache, and depression.
Ginseng	Ginsenosides are thought to be the active ingredients in ginseng. Ginseng has been used as a laxative, tonic and diuretic.
Glucosamine/chondroitin sulfate	Widely used alone and in combination with glucosamine to alleviate pain and inflammation from osteoarthritis.
Goldenseal root	Traditionally used to treat wounds, digestive problems and infections. Current uses include as a laxative, tonic, and diuretic.
Green tea extract	Used for its antioxidative properties.
Gum guggul extract	Used as a dietary supplement and has demonstrated biological effects on lipid metabolism, thyroid hormone homeostasis, female reproductive tissues, endogenous nuclear hormone receptors.
Indole-3-carbinol	Found in Brassica vegetables and marketed as a dietary supplement for cancer chemoprevention.
Kava kava extract	A widely used medicinal herb with psychoactive properties sold as a calmative and antidepressant. A recent report of severe liver toxicity has led to restrictions of its sale in Europe.
Milk thistle extract	Used to treat depression and several liver conditions including cirrhosis and hepatitis and to increase breast milk production.
Pulegone	A major terpenoid constituent of the herb pennyroyal. Has been used as a carminative, insect repellent, nervous system.
Resveratrol	trans-Resveratrol is found in grapes and wine and is currently marketed in pure or extract form as a dietary supplement.
Senna	Laxative with increased use due to the removal of a widely used chemical-stimulant type laxative from the market.
Thujone	Terpenoid is found in a variety of herbs including sage and tansy and in high concentrations in wormwood. Suspected as the causative toxic agent associated with drinking absinthe, a liqueur flavored with wormwood extract.
Usnea lichen	<i>Usnea barbata</i> is used as dietary supplements for weight loss.



## **Selected references and suggested reading:**

Barnes PM, Bloom B, Nahin RL. CDC National Health Statistics Reports Number 12 Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007.

<http://nccam.nih.gov/news/camstats.htm>

Dietary Supplement Fact Sheets available on the NIH Office of Dietary Supplements.

[http://dietary-supplements.info.nih.gov/Health\\_Information/Information\\_About\\_Individual\\_Dietary\\_Supplements.aspx](http://dietary-supplements.info.nih.gov/Health_Information/Information_About_Individual_Dietary_Supplements.aspx)

FDA Consumer Information on Dietary Supplements

<http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/default.htm>

Fu PP, Chiang HM, Xia Q, Chen T, Chen BH, Yin JJ, Wen KC, Lin G, Yu H. (2009) Quality assurance and safety of herbal dietary supplements. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* **27**:91-119.

Matthews HB, Lucier GW, Fisher KD. (1999) Medicinal herbs in the United States: research needs. *Environ Health Perspect* **107**:773-778.

### **Androstenedione**

NTP Draft Report on the Toxicology and Carcinogenesis Studies of Androstenedione (CAS No. 63-05-8) in F344/N Rats and B6C3F1 Mice (Gavage studies) <http://ntp.niehs.nih.gov/go/33416>

### **Gingko**

Gray DE, Messer D, Porter A, Hefner B, Logan D, Harris RK, Clark AP, Algaier JA, Overstreet JD, Smith CS. (2007) Analysis of flavonol aglycones and terpenelactones in *Ginkgo biloba* extract: A comparison of high-performance thin-layer chromatography and column high-performance liquid chromatography. *J AOAC Int* **90**:1203-1209.

### **Ginseng**

NTP Draft Report on the Toxicology and Carcinogenesis Studies of Ginseng (CAS No. 50647-08-0) in F344/N Rats and B6C3F1 Mice (Gavage studies) <http://ntp.niehs.nih.gov/go/34797>

### **Goldenseal**

Etheridge AS, Black SR, Patel PR, So J, Mathews JM. 2007) An *in vitro* evaluation of cytochrome P450 inhibition and P-glycoprotein interaction with goldenseal, *Ginkgo biloba*, grape seed, milk thistle, and ginseng extracts and their constituents. *Planta Med*. **73**:731-741.

NTP Draft Report on the Toxicology and Carcinogenesis Studies of Goldenseal Root Powder (*Hydrastis canadensis* L.) in F344/N Rats and B6C3F1 Mice (Feed studies) <http://ntp.niehs.nih.gov/go/33416>



Weber HA, Zart MK, Hodges AE, Molloy HM, O'Brien BM, Moody LA, Clark AP, Harris RK, Overstreet JD, Smith CS. (2003) Chemical comparison of goldenseal (*Hydrastis canadensis* L.) root powder from three commercial suppliers. *J Agric Food Chem.* **51**:7352-7358.

Weber HA, Zart MK, Hodges AE, White KD, Barnes SM, Moody LA, Clark AP, Harris RK, Overstreet JD, Smith CS. (2003) Method validation for determination of alkaloid content in goldenseal root powder. *J AOAC Int* **86**:476-483.

### Kava kava

Clayton NP, Yoshizawa K, Kissling GE, Burka LT, Chan PC, Nyska A. (2006) Immunohistochemical analysis of expressions of hepatic cytochrome P450 in F344 rats following oral treatment with kava extract. *Exp Toxicol Pathol* **58**:223-236.

Mathews JM, Etheridge AS, Valentine JL, Black SR, Coleman DP, Patel P, So J, Burka LT. (2005) Pharmacokinetics and disposition of the kavalactone kawain: interaction with kava extract and kavalactones *in vivo* and *in vitro*. *Drug Metab Dispos* **33**:1555-1563.

### Milk Thistle

NTP Draft Report on the Toxicology and Carcinogenesis Studies of Milk Thistle Extract (CAS No. 84604-20-6) in F344/N Rats and B6C3F1 Mice (Feed studies) <http://ntp.niehs.nih.gov/go/34797>

### Pulegone

Chen LJ, Lebetkin EH, Burka LT. (2003) Comparative disposition of (R)-(+)-pulegone in B6C3F1 mice and F344 rats. *Drug Metab Dispos* **7**:892-899.

Ferguson LJ, Lebetkin EH, Lih FB, Tomer KB, Parkinson HD, Borghoff SJ, Burka LT. (2007) 14C-labeled pulegone and metabolites binding to alpha2u-globulin in kidneys of male F-344 rats. *J Toxicol Environ Health A* **70**:1416-1423.

NTP Draft Report on the Toxicology and Carcinogenesis Studies of Pulegone (CAS No. 89-82-7) in F344/N Rats and B6C3F1 Mice (Gavage studies) <http://ntp.niehs.nih.gov/go/34797>